## REMARKS

Claims 18-19 are pending in this Application. Claim 18 has been amended to state that the composition comprises at least one nitric oxide production inhibitor. New Claims 37-40 have been added. Upon entry of this Amendment and Response, Claims 18-19, and 37-40 will be pending in this Application.

**Rejection Under 35 USC §112, Second Paragraph**

Claims 18 and 19 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Office Action alleges "In the absence of a structural formula or nomenclatorial description in the claims, the active agent to be used in the method claim has not been particularly pointed out or distinctly claimed." See the Office Action at page 2. The Office Action further alleges that "the instant specification provides no adequate distinction of which particular agent or agents would be indicated for [nitric oxide production] inhibition…." *Id.*

It is noted that all that the patent laws require is that the claims be sufficiently clear that those skilled in the art are able to determine whether a compound of interest is (or is not) within the scope of the claims. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one of ordinary skill can determine what subject matter is or is not within the scope of the claims). As discussed in detail below, Applicant believes that those skilled in the art would have no difficulty in determining whether an agent of interest is or is not within the scope of these claims. Absent reasoning or evidence to the contrary, the claims are definite within the meaning of the patent laws.

It is submitted that the Office Action does not provide any evidence to show why the claims are indefinite. The Office Action merely concludes that "In the absence of a structural formula or nomenclatorial description in the claims, the active agent to be used in the method claim has not been particularly pointed out or distinctly claimed…. [And that] the instant specification provides no adequate distinction of which particular agent or agents would be indicated for [nitric oxide production] inhibition…." See page 2 of the Office Action. These are

merely conclusory statements. The Office Action does not provide any evidence that this is the case. It is submitted that the Office Action must provide evidence(s) showing indefiniteness of the claims. A mere statement in the Office Action concluding that the claims are indefinite cannot be a proper basis of the rejection under 35 U.S.C. §112, second paragraph.

More significantly, one skilled in the art would have no difficulty in determining whether an agent of interest is or is not within the scope of these claims. Pending claims are directed to administering "a composition comprising at least one agent exhibiting mammalian $\alpha_1$-antitrypsin, $\alpha_1$-antitrypsin-like, or serine protease inhibitor activity." It is submitted that such agents are clearly described in the specification, and therefore one of ordinary skill in the art can readily determine whether a particular agent is or is not within the scope of the claims. The term "antitrypsin" derives its name from "ability to inactivate pancreatic trypsin." See page 2, lines 19-20, of the Specification. Accordingly, agents that exhibit $\alpha_1$-antitrypsin or $\alpha_1$-antitrypsin-like activity are those that have ability to inactivate pancreatic trypsin. One skilled in the art can readily determine whether an agent exhibits $\alpha_1$-antitrypsin or $\alpha_1$-antitrypsin-like activity simply by observing its ability to inactivate pancreatic trypsin. Furthermore, the specification clearly lists various characteristics and/or methods for determining whether an agent is within the scope of the claim. For example, on pages 3-4 of the specification it states:

> The $\alpha_1$-antitrypsin-like agent can include, but is not limited to, small organic molecules including naturally-occurring and synthetic molecules, natural products including those produced by plants and fungi, peptides, variants of $\alpha_1$-antitrypsin, chemically modified peptides, and proteins. **An $\alpha_1$-antitrypsin-like agent has the capability of inhibiting the proteolytic activity of trypsin, elastase, kallikrein, and/or other serine proteases**.

(Emphasis added). In addition, a wide variety of agents are known to exhibit mammalian $\alpha_1$-antitrypsin, $\alpha_1$-antitrypsin-like, or serine protease inhibitor activities. See, for example, pages 11-17. Furthermore, one skill in the art can readily determine whether a particular agent exhibits $\alpha_1$-antitrypsin, $\alpha_1$-antitrypsin-like, or serine protease inhibitor activity, for example, simply by conducting an assay to determine the agent's ability to inhibit pancreatic trypsin. Such assay methods are well known to one skilled in the art as shown by the present application as well as those references cited in the present application, for example on pages 11-17.

In view of the above, it is submitted that one skilled in the art can readily determine what subject matter is or is not within the scope of the claims. Therefore, claims are sufficiently defined. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

**Rejection Under 35 USC §103(a)**

*Joint Inventorship*

As an initial matter, the Office Action asserts that the "application currently names joint inventors." See page 3 of the Office Action.

The Application Data Sheet and the filing receipt as well as other documents associated with the Application list only Dr. Leland Shapiro as the inventor. Accordingly, Applicant respectfully requests further clarification of joint inventorship assertion and further requests showing of particular document(s) or evidence(s) that list joint inventorship in the present Application.

*Claim Rejection*

Claims 18 and 19 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,789,395, issued to Amine et al. (hereinafter "Amin et al. reference" or "the '395 Patent"), and U.S. Patent No. 5,885,829, issued to Mooney et al. (hereinafter "Mooney et al. reference" or "the '829 Patent") in view of Zhuang et al., *PNAS USA*, **1997**, *94*, 11875-11880 (hereinafter the "Zhuang et al. reference"). In particular, the Office Action alleges that:

> …it would be prima facie obvious to the skilled artisan at the time of invention to at once recognize the reasonable expectation of success via the combining or the incorporating together of teachings of Amin et al., Mooney et al. and Zhuang. Amin et al. teach methods that inhibit endogenous production of nitric oxide *in vivo, in vitro, or ex vivo* in a mammalian system. Mooney teach [sic] the specific inhibition of serine protease *in vivo* for biocompatibility testing or assaying. Zhuang et al. teach macrophages as cells, which are susceptible to producing nitric oxide. Likewise, these cells were studied in an *in vitro* culture. Instant claim 19 is made obvious by the same testing shared by the above references in relation to mammalian tissue and/or cell cultures and mammalian biocompatibility organ testing.

See page 6 of the Office Action.

The Office Action alleges Amin et al. teach a "*method for inhibiting endogenous production of nitric oxide (NO)...*" using "a *tetracycline compound* to inhibit production of NO

and/or to inhibit the expression or activity of an inducible isoform of nitric oxide synthase (iNOS). Preferably, the tetracycline compound has inhibitory activity for metalloproteinases." Page 3 of the Office Action. But the Office Action admits that "Amin et al. does not teach serine protease and/or antitrypsin." Page 4 of the Office Action.

According to the Office Action "Mooney et al. teach general *serine protease inhibitor 3,4-dichloroisocoumarin* and the specific thiol reagent N-ethyl maleimide were shown to block apoptotic internucleosomal DNA cleavage in thymocytes without the involvement of endonucleases…." *Id.* (Emphasis original). In particular, the Office Action acknowledges that Mooney et al. teach using various apoptosis inhibitors (*Id*); however, nowhere in the Office Action state that Mooney et al. used a nitric oxide inhibitor let alone a nitric oxide inhibitor that exhibits mammalian $\alpha_1$-antitrypsin, $\alpha_1$-antitrypsin-like, or serine protease inhibitor activity.

The Office Action appears to allege that Zhuang et al. teach macrophages are cells that produce nitric oxide. Page 6 of the Office Action. Furthermore, the Office Action asserts that:

> Amin et al. teach the objective of claimed invention in addition to the central issue of claimed invention. Accordingly, Amin et al. serves [sic] as the motivation to combine both Mooney et al. and Zhuang et al. in obviousness over claimed invention.

*Id.*

In contrast to the Office Action, it is submitted that the combination of the cited references does not produce the claimed invention. Pending Claims of the present Application are directed to a method for inhibiting nitric oxide production in cells by using a composition that comprises an agent that exhibits mammalian $\alpha_1$-antitrypsin activity, $\alpha_1$-antitrypsin-like activity, or serine protease inhibitor activity. In contrast, none of the cited references disclose using an agent that exhibits mammalian $\alpha_1$-antitrypsin activity, $\alpha_1$-antitrypsin-like activity, or serine protease inhibitor activity to inhibit production of nitric oxide in cells. Accordingly, combination of the cited references does not produce the claimed invention.

More significantly, it is submitted that combination of the cited references as suggested in the Office Action would teach away from the methods claimed in the presently pending claims. For example, the Office Action states "Amin et al. teach the objective of claimed invention in

addition to the central issue of claimed invention." Page 6 of the Office Action. Furthermore, the Office Action acknowledges that "Amin et al. does not teach [using a] serine protease and/or antitrypsin." Page 4 of the Office Action. In contrast, Amin et al. teach using a compound having inhibitory activity for metalloproteinase for inhibiting nitric oxide production. ("Preferably, the tetracycline compound has inhibitory activity for metalloproteinases." Page 3 of the Office Action.). Accordingly, one skilled in the art would have been motivated to use a compound having inhibitory activity for metalloproteinase in order to inhibit nitric oxide production in cells. In contrast, as stated above, methods of the pending Claims of the present Application use an agent that exhibits mammalian $\alpha_1$-antitrypsin activity, $\alpha_1$-antitrypsin-like activity, or serine protease inhibitor activity to inhibit production of nitric oxide in cells. Therefore, combination of the cited references would teach away from methods claimed in the pending Claims.

In view of the foregoing, it is submitted that the combination of cited references does not lead to methods of the presently pending Claims. Moreover, the combination of the cited references actually teaches one skilled in the art away from methods claimed in the pending Claims. Accordingly, it is respectfully submitted that the rejection of the claims under 35 U.S.C. §103(a) is improper and should be withdrawn.

## Conclusion

In view of the foregoing, it is submitted that all claims now pending in this Application are in condition for allowance. Therefore, an early Office Action to that effect is earnestly solicited. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 303-955-8103.

Respectfully submitted,

Date: January 7, 2008

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